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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,162	08/29/2006	Kornelia Polyak	00530-116US1 DFCI 853.02	5286

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
07/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/550,162	POLYAK ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8-23,26,32,40,50,51,58,64,71,72 and 78-80* is/are pending in the application.

4a) Of the above claim(s) *1,2,9-23,26,32,40,50,51,58,64,71 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 78-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/05; 3/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III, provisionally electing the species of a gene encoding S100A7 in the reply filed on 5/26/09 is acknowledged. The traversal is relative to the species election only. Applicant traversed the species election on the basis of the amendment of the claims, indicating that examination of the currently recited species is preferred. This is being construed as an election of CTSK as the species. Had this species been presented earlier, it would have been given as an option in the restriction requirement. As per applicant's election, claims 8 and 78-80 are examined herein as recited in the instantly pending claim set. The requirement is still deemed proper and is therefore made FINAL.

2. All references to the teachings in the specification by paragraph number utilize the numbering provided in the US pre-grant publication of this application- US 2007/0054271 A1.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 78 and 80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

There is no basis in the specification to support the recitation that CTSK is expressed in stromal cells. There is no basis in the specification to support the recitation that the CTSK gene is expressed at a higher level in invasive cancer cells than in DCIS cells. The portions in the specification that applicant cited for basis for the newly added claims are silent as to the expression of CTSK in stromal cells or the levels of CTSK in invasive cancer cells relative to DCIS cells (see remarks 5/26/09).

5. Claims 8 and 78-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods for determining the likelihood of a breast cancer being a ductal carcinoma in situ or an invasive breast cancer via the analysis of the level of expression of a gene encoding cathepsin K (CTSK). The nature of the invention requires a knowledge that there exists a predictive relationship between the expression levels of CTSK and the type of breast cancer present in a sample.

The specification teaches in Table 16 that CTSK is among genes that encoding secreted and cell surface proteins overexpressed in DCIS myoepithelial cells compared to normal myoepithelial cells. Further, the specification teaches in ¶0204 that expression of CTSK was localized to myofibroblasts in DCIS tumors and was expressed in invasive tumors in myofibroblasts.

The specification generally discusses assays in which one or more of the genes in Table 16 are used to distinguish DCIS from invasive breast cancer (see at least ¶0081).

The specification does not provide any particular guidance or data to demonstrate that CTSK expression differs between DCIS breast cancer cells and invasive breast cancer cells. There is no teaching in the specification that CTSK is expressed in stromal cells.

Littlewood-Evans et al. teach that CTSK is expressed in human breast carcinoma, in particular teaching that four cases of ductal carcinoma in situ accompanying invasive carcinoma or occurring in the absence of invasive disease showed similar CTSK staining patterns, and that hybridization of CTSK mRNA showed a histological pattern of expression similar to that observed for the protein (Littlewood-Evans et al. Cancer Research, Vol. 57, pages 5386-5390, p. 5388).

At the time the invention was made, it had been disclosed that there are extensive similarities at the transcriptome level among distinct stages of the progression of breast cancer. Ma et al. teach that the pathologically discrete stages (ADH, DCIS, and IDC) of breast cancer are highly similar to each other at the level of the transcriptome (Ma et al. PNAS, May 13, 2003, Vol. 100, No. 10, pages 5974-5979). They further teach that this finding supports the idea that the distinct stages of progression are evolutionary products of the same clonal origin, and that genes conferring invasive growth are active in the preinvasive stages. Following this teaching, it was highly unpredictable at the time the invention was made whether or not any quantifiable difference existed between CTSK levels in samples from different stages of cancer.

Further, Lah et al. found that there is diversity in the way that expression levels of different cathepsin variants are distributed in human breast carcinoma, reflecting specific regulation and function of each one during tumor progression (Lah et al. Human Pathology, 2000 Feb; 31(2):149-60). Following this teaching, it is evident that it was highly unpredictable

at the time the invention was made whether or not CTSK expression levels would function as a reliable means to distinguish DCIS from invasive breast cancer. Littlewood-Evans et al. suggested that CTSK should be assessed further as a marker for metastatic potential and outcome of disease in breast cancer, but they do not undertake any study to determine the functionality of CTSK expression as a marker for these. There is no way to whether or not CTSK expression would differ in DCIS relative to invasive breast cancer, and in particular that CTSK expression would differ so significantly so as to be useful for classifying tumor type, as claimed.

The instant claims are directed at classifying a sample, but no data are given in the specification to support the classification method. Slonin teaches that a common problem when developing classification schemes based on differential expression data is 'overfitting' the data (Slonin, Nature Genetics Supplement, Vol. 32, December 2002, pages 502-508) . As a consequence, when using differential expression data to develop classification schemes, classification of the training samples may well be perfect but subsequent attempts to classify new test data fail miserably. Here there has been no attempt to validate a classification scheme based on CTSK alone, and so it remains highly unpredictable as to whether or not classification based on relative expression of this would be successful.

Because some of the claims encompass the classification of breast cancer in any organism, whereas the specification provides only an analysis of human subjects, it is relevant to point out the unpredictability in extrapolating gene expression analysis results from humans to other even closely related animals. Enard et al (2002) teaches that large numbers of quantitative changes in gene expression can be detected between closely related mammals (p.342, middle col., last paragraph; (Enard et al. Science April 2002, Vol. 296, pages 340-343). Thus, even if

one were to establish that the expression of a specific collection of genes is predictive of breast cancer stage in humans, it would not be predictable that the expression of those genes would be predictive in any other organism.

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention due to the lack of any data demonstrating differential expression of CTSK in DCIS and invasive breast carcinoma. In order to practice the claimed invention, one would have to undertake experimentation to establish what, if any, predictive relationship exists in the expression of this gene between these two types of breast cancer. Success is not guaranteed, and indeed the results remain highly unpredictable, as discussed by the references cited. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

Thus, having carefully considered the nature of the invention, the teachings in the specification, the state of the prior art, the level of unpredictability in the technology, and the lack of any working examples to support the claimed invention, it is concluded that it would require undue experimentation to practice the claimed invention.

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Tuesday or Wednesday, from 9:00 AM until 4:30 PM, and Thursday afternoon from 12:30 PM until 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached by calling (571) 272-0763.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

July 15, 2009